STUDIES IN INFLUENZA AND PNEUMONIA

IV. Further Results of Prophylactic Inoculations

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To determine the value of vaccination against disease, it is essential that the disease shall be one which a relatively large number of persons will develop unless protected, and that it be accompanied by serious consequences. These conditions were amply fulfilled during the pandemic of influenza. Moreover, the vaccine should contain the killed bacteria that produce symptoms and which are at least contributory to the cause of death. We have attempted, so far as possible, to fulfil this requirement by making a careful bacteriologic study of the disease, and by incorporating into the vaccine the important bacteria isolated. The epidemic was severe, and the need and the demand for vaccination were great; a large number of cases were available for bacteriologic study and to supply the proper strains for the vaccine. Vaccinations in large numbers during the past ten years with bacteria belonging to the group found in influenza have at least proved harmless, and in the case of pneumonia, prophylactic vaccinations

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have been successfully carried out by Wright,[1] Lister,[2] and Cecil and Austin.[3] A splendid opportunity to study the effect of prophylactic inoculation was at hand. Owing to the foresight of the founders of the Mayo Foundation, necessary funds to meet the emergency were available. A large amount of the vaccine has been prepared and sent gratis on request to numerous physicians on condition that reports of the results be returned.

In a previous report,[4] the reasons for the use of a mixed vaccine containing, as far as possible, freshly isolated strains were discussed. It was pointed out that the streptococci, especially green-producing streptococci from influenza, have certain peculiar properties. The preliminary results, as reported from the use of this vaccine, indicate that considerable protection is afforded against influenza and especially against the accompanying pneumonia. Vaccinations were begun soon after the onset of the epidemic. The period of observation was six weeks. It is our purpose in this paper to emphasize essential points in the preparation of the vaccine, to present further results from its use, and to record certain immunologic experiments.

COMPOSITION AND PREPARATION OF THE VACCINE

Influenza bacilli were isolated in large numbers at the outset of the epidemic, but they were rarely found later in the epidemic. The small fraction of influenza bacilli included in the first few batches of vaccine were therefore omitted, and the vaccine was made to contain a proportionately higher percentage of the green-producing streptococci. In other respects, the original formula has been adhered to. The formula as used in almost all cases covered by the present report is given in Table 1.

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1. Wright, A. E.; Morgan, W. P., et al.: Observations on Prophylactic Inoculation Against Pneumococcus Infections and on the Results Which Have Been Achieved by It, Lancet **1**: 1-10 (Jan. 3) 1914.

2. Lister, F. S.: Prophylactic Inoculation of Man Against Pneumococcal Infections and More Particularly Against Lobar Pneumonia; Including a Report on the Results of the Experimental Inoculation, with a Specific Group Vaccine, of the Native Mine Laborers Employed on the Premier (Diamond) Mine and the Crown (Gold) Mines in the Transvaal and the de Beers (Diamond) Mines at Kimberley—Covering the Period from Nov. 1, 1916, to Oct. 31, 1917, Publications of the South African Institute for Medical Research, Johannesburg, South Africa, W. E. Hortor and Company, Ltd., 1917, pp. 1-30.

3. Cecil, R. L., and Austin, J. H.: Prophylactic Inoculation Against Pneumococcus, J. Exper. M. **28**: 19-41 (July 18) 1918.

4. Rosenow, E. C.: Prophylactic Inoculation Against Respiratory Infections: Preliminary Report, J. A. M. A. **72**: 31-34 (Jan. 4) 1919.

The preparation of the medium, the method of cultivating and collecting the bacteria, and the procedure of standardizing the dose and killing the bacteria are described in the preliminary report.[4] The vaccine, it will be remembered, was made to contain approximately 5 billion bacteria for 1 c.c. Later, the concentration was made twice as great, and the quantity of liquid was reduced to one-half. The injections were given subcutaneously one week apart. The first dose of the concentrated vaccine (0.25 c.c.) contained 2.5 billion, the second (0.5 c.c.) 5 billion, and the third (0.75 c.c.) 7.5 billion bacteria. Considering the large size of these doses and the reactions obtained, the injections should not be given oftener than once a week in order not to overstimulate the mechanism of immunity.

TABLE 1.—FORMULA OF VACCINE

Pneumococci, Types I (10 per cent.), II (14 per cent.), and III (6 per cent.)	30 per cent.
Pneumococci Group IV and the allied green-producing diplostreptococci described	40 per cent.
Hemolytic streptococci	20 per cent.
Staphylococcus aureus	10 per cent.

The tendency of streptococci to undergo changes and to lose specific properties has been repeatedly emphasized by one of us. It was thought important that freshly isolated strains should be included in the vaccine. In Table 2 are given the culture generations of all the strains that have been used throughout the epidemic. The fermentation power was tested of fifty-seven strains of the green-producing streptococci included in the vaccine; only twenty-seven fermented inulin, and only eight were bile soluble.

The advantages which should come from the use of a lipovaccine, particularly when a series of strains needs to be included, have already been pointed out, and a simple method for the preparation in oil of a vaccine of the formula given in Table 1 has been developed and submitted for publication. A further study of the sputum and other material shows that of all the bacteria isolated, the somewhat peculiar green-producing streptococcus or diplostreptococcus is the most important. This organism is present in large numbers at the very outset of symptoms of influenza and of the accompanying pneumonia; it is commonly

present after death. If the sputum or mass cultures are injected intraperitoneally into animals, they die, usually from invasion of the green-producing streptococci or pneumococci. If injected intratracheally in guinea-pigs the picture of influenzal pneumonia is closely simulated. Immunologic experiments with the serum from a horse injected with one strain indicate that most of the strains are immunologically alike. The serum of cases of influenza develops agglutinating power over these strains.

AGGLUTINATING POWER

In Table 3 it is shown that the vaccine used possessed well marked antigenic powers. The strains S 1, S 3, 2598[2].2, 2604.2, 3048.3, and 2874[2].3 were green-producing streptococci or pneumococci; 2575.2, a hemolytic streptococcus, and 2608[3].2, a staphylococcus from cases of influenza. It will be noted that agglutinins appear in the serum on the tenth day and persist for six weeks. Table 3 shows, moreover, that

TABLE 2.—CULTURE GENERATION OF BACTERIA FROM INFLUENZA AS USED IN THE VACCINE

Cultures	Green-Producing Streptococcus	Hemolytic Streptococcus	Staphylococcus
Third generation or below.....	58	18	18
Fourth to tenth generation.....	95	20	8
Eleventh to twentieth generation.	21	0	0
Total.....	174	38	26

the bacteria in the vaccine (492) used as the antigen in the first column were susceptible to agglutination. This vaccine was prepared three months previously and was kept in the ice chest. Most of the strains used as antigen in the experiment recorded in this table were not included in the vaccine used to immunize the persons whose serums were tested. All the green-producing streptococci were agglutinated, however, by the monovalent horse serum.

In Table 4 are given the results following the injection of a single dose of the lipovaccine (from 25 to 75 billions) in three persons. It may be noted that the amount of agglutination is greater than that following the injection of the saline vaccine, but here, as in the

TABLE 3.—AGGLUTINATING POWER OF THE SERUM OF PERSONS INOCULATED WITH SALINE VACCINE

Serums (Dilutions 1:20)	Strains								
	492	S 1	S 3	2,598[2].2	2,604.2	3,048.3	2,874[2].3	2,575.2	2,608[3].2
2,542 24 hours before third dose saline vaccine	0	0	0	0	0	+	+	0	0
2,542 24 hours after third dose saline vaccine	0	0	0	0	0	+	+	0	0
2,542 48 hours after third dose saline vaccine	0	0	0	0	++	++	++	0	0
2,542 10 days after third dose saline vaccine	+	++	+	0	++	++	+++	++	0
2,542 6 weeks after third dose saline vaccine	+	++	..	..	++	..	..	..	0
2,543 24 hours before third dose saline vaccine	0	0	0	0	+	0	0	0	0
2,543 24 hours after third dose saline vaccine	0	0	0	0	+	0	0	0	0
2,543 48 hours after third dose saline vaccine	+	0	0	0	++	0	++	0	0
2,543 10 days after third dose saline vaccine	++	+	0	0	++	++	+++	+	+
2,543 6 weeks after third dose saline vaccine	++	+	0	0	+++	++	++	+	0
2,545 24 hours before third dose saline vaccine	0	0	0	0	0	0	0	0	0
2,545 24 hours after third dose saline vaccine	0	0	0	0	0	0	0	0	0
2,545 48 hours after third dose saline vaccine	0	0	0	0	+	0	0	0	0
2,545 10 days after third dose saline vaccine	++	0	0	0	++	++	++	++	++
2,545 6 weeks after third dose saline vaccine	++	0	0	+	++	++	++	++	++
2,547 24 hours before third dose saline vaccine	0	0	0	0	0	0	0	0	0
2,547 24 hours after third dose saline vaccine	0	0	0	0	0	0	0	0	0
2,547 48 hours after third dose saline vaccine	+	0	0	0	+	+	+++	0	0
2,547 10 days after third dose saline vaccine	++	0	+	+	++	++	++	0	0
2,547 6 weeks after third dose saline vaccine	++	0	+	+	++	++	++	0	++
3,075 normal	0	0	0	0	0	0	0	0	0
3,076 normal	0	0	0	0	0	0	0	0	0
NaCl	0	0	0	0	0	0	0	0	0

case following the injection of the saline vaccine, not all strains are equally susceptible to agglutination, and some are not agglutinated at all.

TABLE 4.—AGGLUTINATING POWER OF THE SERUM OF PERSONS INOCULATED WITH LIPOVACCINE

Serums (Dilutions 1:20)	Strains						
	3,271².3	3,296².2	3,331	3,332.2	3,334.2	3,334.2	3,342
3,074 normal	0	++	+	+	0	++	0
3,074 4 days after lipovaccine	+	+++	++	++	+	++	0
3,074 10 days after lipovaccine	+++	++++	+++	++	++	+++	0
3,074 6 weeks after lipovaccine	++	+++	++	+	+	++	0
3,075 normal	0	++	0	0	+	0	0
3,075 4 days after lipovaccine	++	+	0	0	+	++	0
3,075 10 days after lipovaccine	+	++++	+	+	++	++	0
3,076 normal	0	++	+	0	0	0	0
3,076 4 days after lipovaccine	+	+++	+	0	+	0	0
3,076 10 days after lipovaccine	++	+++	++	0	+	0	0
3,076 6 weeks after lipovaccine	+++	++++	+	0	++	0	0
NaCl	0	0	0	0	0	0	0

Table 5 shows the agglutinating power of various immune horse serums over strains of green-producing streptococci from influenza, strains included in the vaccine. The serum from Horse 15, immunized with one strain from the blood of a patient who died, has marked agglutinating power over most of the strains. Of the thirty-three strains tested in this manner, twenty-five were agglutinated specifically by this serum. The results indicate clearly that among the green-producing streptococci, including Group IV pneumococci in influenza, there are strains which have a specific relationship, and that we were fortunate in successfully separating them from the ordinary *Streptococcus viridans* and including them in the vaccine long before the results of immunologic experiments were available.

The apparent protection against attacks of influenza noted in the preliminary report, difficult to understand at that time, now becomes rational.

METHOD OF SECURING DATA

In most instances the reactions were mild, about one person in each 100 reacted more severely. Some reacted severely to all three inoculations, others only

TABLE 5.—AGGLUTINATING POWER OF VARIOUS IMMUNE HORSE SERUMS OVER STREPTOCOCCI INCLUDED IN THE VACCINE

Serums (Dilutions 1:20)	Strains														
	2,347.19	2,349.13	2,350.16	2,531.14	2,532.4	2,534.11	2,557.2	2,604.2	2,618[2].2	2,684.16	2,698[2].3	2,719[2]	2,769	2,800[2].2	2,825
Pneumococcus Type I....	0	0	0	+	0	0	0	0	0	0	0	0	0	0	0
Pneumococcus Type II...	++	0	0	+	0	+	0	0	0	++	0	0	0	0	0
Pneumococcus Type III..	0	0	0	+	0	+	0	0	0	0	0	0	0	0	0
Horse 9.....	++	++	0	+	0	++	0	0	0	0	0	+++	0	0	++
Horse 15.....	++++	+++	++++	++++	+++	++++	0	+++	++++	++	++++	++	0	++	+++
Normal horse.....	0	0	0	+	0	+	0	0	0	0	0	0	0	0	0
NaCl.....	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

TABLE 6.—RESULTS AS REPORTED IN QUESTIONNAIRES FROM ALL SOURCES

Groups	Total Number	Incidence for 1,000 Persons									
		Disease				Deaths					
		Influenza	Acute Edema of Lungs	Pneumonia	Empyema	Acute Edema of Lungs	Pneumonia	Empyema	Meningitis	Encephalitis	Total Deaths
Vaccinated once...	26,936	118.2	3.1	8.7	0.29	0.14	2.6	0.07	0.18	....	3.0
Vaccinated twice..	23,348	97.0	0.77	3.04	0.17	0.47	1.9	0.04	0.21	....	2.62
Vaccinated 3 times	93,476	87.9	0.8	4.4	0.18	0.18	1.2	0	0.05	....	1.43
Not vaccinated....	345,133	281.8	4.4	21.0	0.83	1.7	2.37	0.07	0.15	0.03	8.55

to one or two. Persons coming down with a cold or with symptoms of influenza are often hypersensitive. Marked diffuse redness resembling erysipelas about the site of inoculation, with swelling and, later, marked induration, has occurred occasionally. In no instance were the symptoms alarming. The number of severe reactions is sufficiently large, however, to prevent general vaccination except at the time of an acute emergency. This is in accord with the experience of Cecil and Austin,[3] noted during prophylactic inoculations with pneumococci. An outline for records of persons vaccinated was sent with each batch of vaccine and later a questionnaire. The questionnaire asked for the date of the onset of the epidemic, the date when the vaccine was first used, the week of the height of the epidemic, the week in which the greatest number of vaccinations were given, and the duration of the epidemic. The number of cases of influenza from the time the vaccinations were begun until the end of the epidemic, or up to May 1, and the number of deaths which occurred among the vaccinated and unvaccinated in the same period, in the practices of the physicians supplied with the vaccine, were asked. The reports of the use of the vaccine after the epidemic had disappeared were excluded. The period of observation in most instances was from four to five months.

In determining a safe criterion as to the value of the vaccine, we have purposely been unfair to the vaccinated group. The protection afforded among the vaccinated patients was measured from the day of the first vaccination, whereas, judging by the agglutination experiments, it should be calculated from about one week after the third injection.

There is another reason why we have arbitrarily decided to make our calculations from the day of the first vaccination. A procedure, calculated to protect against an epidemic disease, such as influenza, should have sufficient protective value when given after the onset of the epidemic to be measurable, for it is practically impossible to anticipate these epidemics and, moreover, persons will not present themselves for vaccination until the epidemic is at hand.

The questionnaire was arranged so as to yield information regarding the incidence of influenza, acute

edema of the lungs, pneumonia and empyema, and the deaths from acute edema of the lungs, pneumonia, empyema, meningitis, and encephalitis among the vaccinated and the unvaccinated. Separate reports including the foregoing points were asked for from institutions and in the cases of pregnant women. The impressions gained from the use of the vaccine regarding the severity of the disease if contracted following vaccination, and the effect, if any, which the vaccine had on certain chronic infections, such as bronchitis, sinusitis, myositis, and arthritis were asked for.

Many physicians were so overwhelmed during the height of the epidemic that accurate records could not be kept, and accordingly the reports containing accurate data are proportionately few. The reports of 530 physicians were fairly complete, however, and these are summarized in Table 6. It is realized that there must necessarily be errors in the morbidity figures as reported to us, just as in the case of reports to boards of health. It is generally agreed that as influenza became more prevalent and less severe, a proportionately smaller number of cases were reported, and that all morbidity figures reported are well below the actual figures. The error, however, among the vaccinated and unvaccinated groups in the reports to us, should be approximately the same, and hence the figures should be comparable. Mortality figures, on the other hand, may be considered as fairly accurate.

RESULTS OF INOCULATION

The total number of unvaccinated persons recorded in Table 6 represents the sum of the estimated clienteles of the various physicians reporting the cases, and averages about 1,200 for each. It will be noted that the incidence of influenza, of acute edema of the lungs, of pneumonia following influenza, and the number of deaths from all causes among the vaccinated are consistently lower than that among the unvaccinated. Moreover, the incidence of disease and deaths is lowest in the group of 93,476 persons who were vaccinated three times. The reports included in this table were from many states, but the largest number came from Iowa, Minnesota, and Wisconsin. Thirteen thousand, six hundred and fifty persons inoculated and 2,083 who died were grouped according to age by decades. The

curves indicating the percentage in each run roughly parallel.

The largest number of inoculations were given and the largest number of deaths occurred between the ages of 11 and 40 years. The percentages of the former in these three decades were 23, 19, and 21, of the latter 13, 29, and 23, respectively. Through the cooperation of the Board of Health of Minnesota we were able to check the results as reported to us with the morbidity and mortality figures as reported to them. Reports on a considerable number of vaccinations were received from Brown, Chippewa, Clay, Dodge, Fillmore, Goodhue, Houston, Itasca, Lesueur, Lyon, Mower, Olmsted, Rice, Stearne, Steele, Wabasha, Waseca, Watonwan, and Winona counties. The total estimated population of these counties is 472,584. The total number of cases of influenza in these counties reported to the board of health from the beginning of the epidemic until May 1 is 30,763, or sixty-five for each thousand. This is admittedly a low figure. The total mortality rate as reported to the board of health during this time is 4.2. The mortality rate, excluding the deaths which occurred in the respective counties prior to the date of the first vaccinations, is 3.2 (Table 7). The figures in the table indicating the cases and the deaths as reported to us are believed to be more accurate. The mortality rate, exclusive of that of the Mayo Clinic, in the 17,532 persons vaccinated three times is only one fourth of that reported to the board of health. Moreover, the total number of deaths among the vaccinated, including the persons inoculated only once and twice, is 1.6 for 1,000, or half the mortality rate as reported to the board of health during the same period of time. When we consider the fact that the deaths in each group were counted from the time the first vaccinations were given, which is really unfair to the vaccine, and the fact that our figures include all pneumonias, while those of the board of health include only the influenzal pneumonias, there seems little doubt that the difference must be due to the protection afforded by the vaccine. The figures given in Table 8 for Olmsted County, where about one third of the population was vaccinated, exclusive of the Mayo Clinic and the state hospital, are similar to those obtained elsewhere.

TABLE 7.—RESULTS AS REPORTED IN QUESTIONNAIRES FROM NINETEEN COUNTIES IN MINNESOTA EXCLUSIVE OF THE MAYO CLINIC

Groups	Total Number	Incidence for 1,000 Persons — Disease: Influenza	Disease: Acute Edema of Lungs	Disease: Pneumonia	Disease: Empyema	Deaths: Acute Edema of Lungs	Deaths: Pneumonia	Deaths: Empyema	Deaths: Meningitis	Deaths: Encephalitis	Total Deaths
Vaccinated once...	4,828	115.1	0.4	8.28	0	0	0.2	0	0	0	0.2
Vaccinated twice..	4,029	88.3	0.74	3.7	0.47	0.47	1.9	0	0.47	....	3.2
Vaccinated 3 times	17,532	102.8	0.17	4.2	0.22	. . .	0.62	....	....	....	0.8
Not vaccinated....	36,100	373.5	1.35	20.4	0.6	1.4	4.0	0.13	0.16	0.02	6.35
As reported to State Board of Health..... (Estimated population)	472,584	65.3	....	....	....	. .	....	....	....	....	3.2*

* Exclusive of deaths which occurred prior to the use of the vaccine and exclusive of the Mayo Clinic cases.

TABLE 8.—RESULTS IN OLMSTED COUNTY EXCLUSIVE OF MAYO CLINIC AND STATE HOSPITAL FOR INSANE

Groups	Total Number	Incidence for 1,000 Persons — Disease: Influenza	Disease: Acute Edema of Lungs	Disease: Pneumonia	Disease: Empyema	Deaths: Acute Edema of Lungs	Deaths: Pneumonia	Deaths: Empyema	Deaths: Meningitis	Deaths: Encephalitis	Total Deaths
Vaccinated once...	2,424	100.2	0	6.1	0	0.41	2.8	0	0	0	3.2
Vaccinated twice..	1,021	291.8	2.9	0	1.9	0	4.8	0	1.9	....	6.7
Vaccinated 3 times	9,300	41.0	0.18	3.9	0.43	....	0.43	0.21	....	....	0.64
Not vaccinated....	8,700	248.0	3.2	13.1	0.45	0.9	2.6	0.45	0.12	....	4.0

The incidence of disease and the death rate among those vaccinated three times are well below that of those not vaccinated.

The results obtained in institutions in which the conditions among the vaccinated and the unvaccinated were comparable are summarized and given in Table 9 in order still further to check the figures. The number of persons in most of the institutions included (fifty-three in all) was small. The opportunity for accurate observation was, therefore, favorable. The institutions included factories, personnel of hospitals, schools, and offices. The proportion of the vaccinated and unvaccinated varied between wide limits. The period of observation in the two groups was the same. The

TABLE 9.—RESULTS OF PROPHYLACTIC INOCULATION IN INSTITUTIONS WHERE THE CONDITIONS AMONG THE VACCINATED AND UNVACCINATED WERE COMPARABLE

		Incidence for 1,000 Persons					
		Disease				Deaths	
Groups	Total Number	Influenza	Acute Edema of Lungs	Pneumonia	Empyema	Acute Edema of Lungs	Pneumonia
Vaccinated 3 times	8,306	31	0.1	1.0	0.2	0	0.5
Not vaccinated....	9,388	200	0.5	12.0	0.6	0.4	5.5

incidence of disease and the number of deaths in almost all instances were lower in the vaccinated than in the unvaccinated group. The total average, as given in Table 9, compares favorably with that of the others. The death rate among the vaccinated is decidedly lower than among the unvaccinated.

The results given in the tables are in agreement with the numerous reports received by which it appeared that the vaccine had afforded striking instances of protection. In a few cases no protection seemed to be afforded, but in most of these the vaccinated persons contracted the disease a long time after the inoculations. It is fully realized how difficult it is to judge just how much protection was conferred in many of these instances, and how much of the apparent protection was merely coincidental. But a careful study of the reports from 303 physicians, some of which were the result of careful observation, forces the conviction that real protection, especially against pneumonia, was afforded. In some of these instances most of the

TABLE 10.—RESULTS OF PROPHYLACTIC INOCULATION IN PREGNACNY

Groups	Total Number	Incidence for 1,000 Persons — Disease: Influenza	Disease: Acute Edema of Lungs	Disease: Pneumonia	Disease: Empyema	Disease: Miscarriage	Deaths: Acute Edema of Lungs	Deaths: Pneumonia	Deaths: Empyema	Deaths: Meningitis	Deaths: Total Deaths	Mortality of Those Who Developed Influenza
Vaccinated 3 times	997	109.3	17.0	27.0	....	14.0	2.0	12.0	....	....	14.0	12 per cent.
Not vaccinated....	3,656	294.6	17.7	80.4	0.82	46.2	12.3	46.2	0.54	0.82	59.9	20 per cent.

observations were made within six weeks to two months after the vaccine was given.

It was thought that the injection of large doses of a mixed vaccine might have some effect on certain chronic infections, especially of the respiratory tract. A summary of the reports shows that 961 persons with chronic bronchitis were benefited and that thirty-eight were made worse. The reports show that 127 persons with chronic sinusitis were benefited and four made worse. Improvement was noted in 121 persons having myositis and in 129 with arthritis, while in one of the former and in twenty-two of the latter the symptoms were aggravated. These figures are not considered to be especially significant but worthy of record. They are in accord with our own observations.

RESULTS OF PROPHYLACTIC INOCULATION IN PREGNANCY

The results of vaccinations in pregnant women as reported in the questionnaires are summarized in Table 10. The incidence of disease and that of miscarriages and the mortality rate are consistently lower among those vaccinated than among those not vaccinated. The mortality (20 per cent.) of the unvaccinated pregnant women who developed influenza is somewhat lower than that reported from similar statistical studies by Bland[5] and by Harris.[6] They report a mortality of 37.7 per cent. and 27 per cent., respectively. The mortality of 12 per cent. in the 997 pregnant women inoculated in our series is in sharp contrast and calls for a further trial of this measure.

Almost from the beginning of the epidemic of influenza, patients who registered at the Mayo Clinic were advised to be vaccinated. From October 1 to May 1, 55,189 patients registered. Of these, 2,542 were vaccinated once, 1,030 twice, and 1,850 three times, a total of 5,422. A reliable morbidity and mortality rate for each thousand of the vaccinated and unvaccinated could not be determined because such a large percentage of patients remained in Rochester for too short a time.

5. Bland, P. B.: Influenza in Its Relation to Pregnancy and Labor, Am. J. Obst. **79**: 184-197 (Feb. 19) 1919.

6. Harris, J. W.: Influenza Occurring in Pregnant Women, J. A. M. A. **72**: 978-980 (April 5) 1919.

It was thought that a study of the cases of influenza admitted to the hospitals might, however, be worth while. Of these, 749 were undoubted cases of influenza, and were analyzed from various standpoints. Fifty-nine of the patients were vaccinated once; twenty-four, twice, and fifty-seven, three times, while 609 were not vaccinated. The incidence of pneumonia and the deaths from pneumonia in these groups are recorded in Table 11. The average interval between the vaccinations and the onset of influenza was nine days in those vaccinated only once, twenty-six days in those vaccinated twice, and forty-five days in those vaccinated three times. The average temperature was more than one degree higher in the unvaccinated than in the vaccinated, and the average duration of fever nearly two days longer. The percentage incidence of pneumonia in those vaccinated three times was 21; in those not vaccinated, 57, while the percentage of deaths

TABLE 11.—RESULTS IN CASES OF INFLUENZA ADMITTED TO HOSPITALS IN ROCHESTER

Groups	Cases of Influenza	Incidence of Pneumonia	Deaths from Pneumonia, per Cent.
Vaccinated once	59	39	10
Vaccinated twice	24	95	12
Vaccinated three times	57	21	5
Not vaccinated	609	57	22

from pneumonia was 5 in the former group and 22 in the latter. The mortality from pneumonia of those vaccinated only once and those vaccinated twice is also well below that of the unvaccinated. The mortality figure in the unvaccinated is abnormally high because only the patients with relatively severe attacks were admitted to the hospitals.

The greater tendency to the development of pneumonia in influenza among the unvaccinated group as observed in this series is in keeping with the lower incidence of this complication (4.7 per cent.) in 11,325 cases of influenza in which the vaccine was given after the onset of the symptoms, as compared with the incidence (8.7 per cent.) in 41,788 cases in which the vaccine was not used. The average mortality in the cases in which the vaccine was used in treatment was 1.4 per cent.; in those not treated it was 2.1 per cent.

From these results considerable weight may be attached to the opinion of nearly all the 430 physicians who have used the vaccine and who have reported on this point, an opinion in agreement with our own observations, that is, that the attacks of influenza if contracted following vaccination are milder and of shorter duration.

SUMMARY

The immunologic and animal experiments reported[7] elsewhere indicate that the mixed vaccine used by us contained the important bacteria as they occur in influenza and the accompanying pneumonia, and that a relatively large number of strains of the green-producing streptococci which appear to have a specific relationship to the initial attack were included. The reports included results obtained under the most varied conditions, from many communities covering a wide range of territory. In some communities the mortality rate was excessively high, in others comparatively low. The number of persons inoculated is sufficiently large to make the statistical figures fairly accurate. The period of observation was from three to seven months. The incidence of influenza and pneumonia as reported to us is probably far from exact, but the percentage of error should be about the same in the vaccinated and unvaccinated groups. Indeed, if a difference exists, the number of cases reported among the vaccinated might be expected to be proportionately higher because, even though no protection was promised, the fact that influenza occurred after the vaccinations were taken would naturally lead to a higher percentage of reports to the physician who gave the inoculations. The average incidence of influenza and pneumonia in the group inoculated three times is about one-third that of the uninoculated group.

The average mortality rate in the uninoculated, as reported to us, approximates the mortality rate (5.4 per cent.) of sixteen large cities of the United States as given in *Public Health Reports* for February 7. The average mortality rate in the group inoculated

7. Rosenow, E. C.: The Experimental Production of Symptoms and Lesions Simulating Those of Influenza with Streptococci Isolated During the Present Epidemic, Study II, J. A. M. A. **72**: 1604-1608 (May 31) 1919. The Occurrence of a Pandemic Strain of Streptococcus During the Pandemic of Influenza, Study III, ibid. pp. 1608-1609.

three times is about one-fifth that of the uninoculated. A definite although a smaller degree of protection appeared to be afforded to those who took only one or two inoculations. From a study of a series of hospital cases of influenza it is found that the tendency to the development of pneumonia in the vaccinated is about one third as great as among the unvaccinated, and that the mortality in the former is about one fifth as great as in the latter. The number of completed vaccinations in pregnant women is not large enough to give exact figures, but the results indicate clearly that a definite degree of protection was afforded in this group of individuals.

It appears from all the facts at hand that by the use of a properly prepared vaccine it is possible to rob influenza of some of its terrors.

The preliminary results from the use of more than 500 doses of this vaccine suspended in oil, the immunologic studies and the results from the use of pneumococcus lipovaccine reported by Fennel[8] and by Cecil and Vaughan[9] suggest strongly that both the degree of protection and the duration of the immunity may be materially increased by the use of lipovaccine over that reported in this paper from the use of the saline vaccine.

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8. Fennel, E. A.: Prophylactic Inoculation Against Pneumonia, J. A. M. A. **71**: 2115-2120 (Dec. 28) 1918.

9. Cecil, R. L., and Vaughan, H.: Results of Prophylactic Vaccination Against Pneumonia at Camp Wheeler, J. Exper. M. **29**: 457-483 (June) 1919.

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